ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2021.46855
Nam Kem Med J 2021;9(2):101-107

Comparison of Biopsy, Computed Tomography and Magnetic Resonance Imaging in the Detection of Hepatosteatosis in Live Liver Donor Candidates

Canlı Karaciğer Donör Adaylarında Hepatosteatozun Saptanmasında Biyopsi, Bilgisayarlı Tomografi ve Manyetik Rezonans Görüntülemenin Karşılaştırılması

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ABSTRACT

Aim: The presence of hepatosteatosis (HS) in the donor has negative effects on the results of liver transplantation (LT). Therefore, the detection of donor HS is vital during the pre-transplant period. The aim of this study was to compare the efficacy of liver biopsy and radiological methods in the detection of HS in live liver donor candidates.

Materials and Methods: Two hundred twenty-six healthy individuals who were admitted to Demiroğlu Bilim University as donor candidates for LT were included in the study. Demographic, histopathological, laboratory and imaging findings of the donors were retrospectively reviewed. Computed tomography (CT) and magnetic resonance imaging (MRI) scans of the donors were retrospectively reevaluated and liver fat measurements were recorded.

Results: 39% (88) of the patients were female and 61% (138) were male. In the study population, the mean age was 34.3±8.7 years, the mean weight was 78.0±12.6 kg, the mean height was 169.1±9.6 cm, and the mean body mass index was 27.2±4.0. 42% of donors had <5% HS, and 58% of donors had >5% HS in liver biopsy. Both CT and MRI showed significant correlations with biopsy in HS detection ($p<0.05$).

Conclusion: In our study, it was found that MRI correlated with biopsy as much as CT and could be used easily in the detection of HS. The use of MRI in liver donors may be more appropriate for donor health prior to transplantation.

Keywords: Liver transplantation, donor steatosis, hepatosteatoz, computed tomography, magnetic resonance imaging

ÖZ

Amaç: Karaciğer donöründe hepatosteatoz (HS) varlığı, karaciğer transplantasyonu sonuçları üzerinde olumsuz etkilere sahiptir. Bu nedenle, donörde HS'nin tespiti, nakil öncesi dönemde hayati önem taşımaktadır. Bu çalışmanın amacı, canlı karaciğer donör adaylarında HS'nin saptanmasında karaciğer biyopsisi ve radyolojik yöntemlerin etkinliğini karşılaştırmaktır.

Gereç ve Yöntem: Demiroğlu Bilim Üniversitesi'ne karaciğer transplantasyonu için donör adayı olarak kabul edilen 226 sağlıklı birey çalışmaya dahil edildi. Donörlerin demografik, histopatolojik, laboratuvar ve görüntüleme bulguları retrospektif olarak incelendi. Donörlerin bilgisayarlı tomografi (BT) ve manyetik rezonans görüntüleme (MRG) taramaları geriye dönük olarak yeniden değerlendirildi ve karaciğer yağ ölçümleri kaydedildi.

Bulgular: Hastaların %39'u (88) kadın, %61'i (138) erkekti. Çalışma popülasyonunda ortalama yaş 34,3±8,7 yıl, ortalama ağırlık 78,0±12,6 kg, ortalama boy 169,1±9,6 cm ve ortalama vücut kitle indeksi 27,2±4,0 idi. Karaciğer biyopsisinde donörlerin %42'sinde <%5 HS vardı ve donörlerin %58'inde >%5 HS vardı. Hem BT hem de MRG, HS saptamada biyopsi ile anlamlı korelasyon gösterdi ($p<0,05$).

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Received: 10.12.2020 **Accepted**: 06.02.2021

Sonuç: Çalışmamızda MRG'nin BT kadar biyopsi ile ilişkili olduğu ve HS'nin saptanmasında rahatlıkla kullanılabileceği bulunmuştur. Karaciğer donörlerinde MRG kullanımı, iyonizan radyasyon içermemesinden dolayı nakil öncesi donör için daha uygun bir yöntem olabilir.

Anahtar Kelimeler: Karaciğer transplantasyon, donör steatoz, hepatosteatoz, bilgisayarlı tomografi, manyetik rezonans görüntüleme

INTRODUCTION

Liver transplantation (LT) is accepted as a revolutionary treatment option for end stage liver disease (ESLD). Donor hepatosteatosis (HS) is one of the major risk factors that adversely affect post-transplant outcomes. HS in donors is common in both deceased and living donor liver transplantation (LDLT). Many transplant centers generally accept cadaveric liver donors with HS up to 30%[1]. Similar criteria are used for LT from living donors. Nowadays, 10-30% HS levels are acceptable for many transplant centers in LDLT[2]. However, >60% liver HS is closely related to primary liver non-function (PNF) at recipients after LT[3,4] and prolongs the donor healing process after LT. Therefore, the detection of donor HS is one of the most important points for LDLT[5].

Currently, invasive liver biopsy is accepted as the gold standard method for the detection of HS but it has some limitations such as complications, high cost, and sampling errors. A non-invasive method is desirable in the diagnosis of HS in order to avoid the risk of liver biopsy. Moreover, histopathological evaluation may show significant differences among pathologists[6]. Many radiological methods have been used for the non-invasive detection of HS, such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). US is an easy, cheap, non-invasive and simple method for this purpose. Although the presence of HS can be detected with US, the rate of fatty accumulation in the liver cannot be measured quantitively. US has also some limitations depending on operator. It also has limited sensitivity, specificity and reliability in obese patients and relatively low levels of HS[7,8].

CT fat quantification has undesired radiation exposure for healthy donor candidates. This method is based on the reverse correlation between liver fat content and liver attenuation which is measured by reduced parenchymal attenuation values in Hounsfield units (HU). Many studies have evaluated the accuracy and sufficiency of CT scan in the detection of HS in living liver donor candidates[9-12].

MRI with different techniques was used to detect HS with high sensitivity and specificity. It is considered by many researchers as one of the most adequate methods for the noninvasive measurement of HS. However, MRI is an expensive and time-consuming radiological method and these disadvantages limit its usefulness[13,14].

The aim of this study was to compare the biopsy, CT and MRI findings in the detection and quantification of HS in live liver donor candidates.

MATERIALS AND METHODS

This study was approved by the institutional review board and protocol review committee of Demiroğlu Bilim University (2019-16-03). Two hundred and twenty-six live liver donor candidates with varying degrees of HS confirmed by biopsy between January 2004 and January 2019 were included in this retrospective study. Patients who had acute and/or chronic viral hepatitis (hepatitis A, B or C), autoimmune, drug-induced or metabolic liver disease, and whose CT and MRI were inadequate for measurements were excluded from the study. The demographic, laboratory, CT and MRI findings of the patients were retrospectively reviewed and recorded from the hospital central information system. All donor candidates underwent a non-contrast upper abdomen and post-contrast triphasic CT imaging protocol with 16-detector MDCT (multidetector CT). (Somatom Sensation - Siemens Medical Systems, Forchheim, Germany). HS evaluation was made from unenhanced CT sections. The median time interval between liver biopsy and imaging (MRI and CT) was 9 days (range, 0-128 days). MRI and CT scans of the patients were performed on the same day.

While <5% HS levels were accepted normal, >5% HS levels were accepted as fatty liver according to biopsy results. Liver attenuation index (LAI) was used to calculate the degree of HS. Density measurements were performed on average 20 region of interest (ROI) in the liver and 10 ROI in the spleen for the evaluation of HS. Areas away from the vascular structures were selected for density measurements in both organs. LAI was calculated by subtracting mean splenic density from mean hepatic density. LAI >5 was accepted as steatosis <5%, 5>LAI>-10 was accepted as steatosis between 5% and 30%, and LAI<-10 was accepted as steatosis >30% (Figure 1)[15].

MR cholangiopancreatography (MRCP) was performed to evaluate biliary anatomy and variations of all donors in preoperative period. MR images were obtained on a 1.5 Tesla MR device (Siemens Magnetom Symphony, 1.5 T MRI System, Erlangen, Germany) using a 4-channel abdominal coil. In phase (IP) and out of phase (OP) images were taken in order to evaluate liver fatty tissue during the MRCP examination.

Chemical shift imaging (CSI) protocol: IP and OP MR images were obtained in sagittal projection (IP time to repeat/time to echo (TR/TE): 118/5.27, OP TR/TE: 118/2.35). In CSI, the matrix selected was 270×512 mm, number of acquisition=1 and field of view=256×256 mm, the cross-sectional thickness was 5 mm,

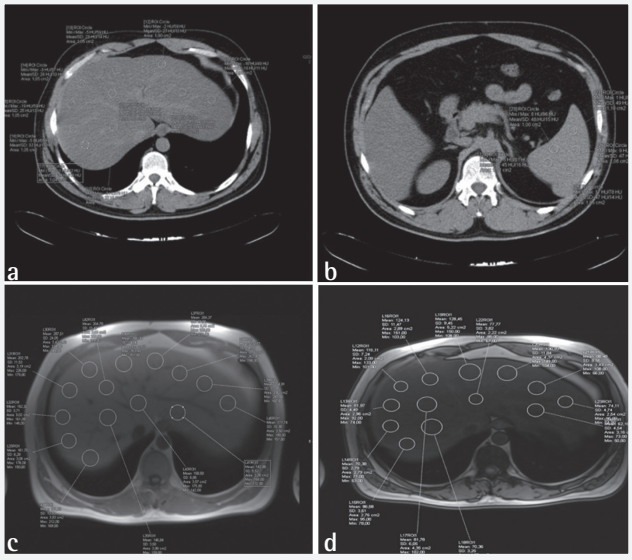

Figure 1. Images of a 35-year-old male who is a candidate for liver donor with hepatostaetosis. (a, b) Unenhanced transverse CT images are shown. HU was measured with ROI from the liver and spleen. The mean pancreatic and splenic CT attenuation was 37 and 47 HU, respectively. The liver attenuation index was found <-10 and was accepted as steatosis >30%. Check the mean SI for the mean measurements made on the MRI in-phase and out of-phase sequences (c, d). The percentage of hepatosteatosis found to be mean 165 SI (IP) and mean 75 SI (OP) was calculated to be 27%.

CT: Computed tomography, HU: Hounsfield unit, ROI: Region of interest, MRI: Magnetic resonance imaging, IP: In phase, OP: Out of phase, SI: Signal intensity

and the cross-sectional range was 0.5 mm. No contrast agents were applied during the examination.

The ROI was determined from IP and OP images and signal intensity (SI) measurements were performed quantitatively. ROIs were inserted avoiding from major intrahepatic vascular structures. An average of 20 measurements were taken from the liver parenchyma on IP and OP images. Then, liver fat ratio was calculated according to the following formula: Fat ratio=(IP-OP/2xIP)x100[16].

Statistical Analysis

SPSS 21.00 for Windows program was used for statistical analysis. As descriptive statistics, the number, percentage for categorical variables, and mean, standard deviation were given. Correlation analysis was performed using the Spearman correlation test. Data with normal distribution were calculated with the Student's t-test and data without normal distribution were calculated using the Mann-Whitney U test. Categorical data were calculated using the chi-square test. Significance level was accepted as $p<0.05$.

RESULTS

Two hundred and twenty-six donors were included in the study. Eighty-eight donors were female (39%) and one hundred and thirty-eight donors were male (61%). The mean age was 34.3±8.7 years, the mean height was 169.1±9.6 cm, and the mean weight was 78.0±12.6 kg. The mean body mass index (BMI) was 27.2±4.0 (Table 1). Complete blood count and laboratory findings of study population were shown in Table 2. The donors

Table 1. General demographic characteristics of the patients

	Mean±SD	Min-Max
Age	34.3±8.7	19-57
Gender		
Female	88 (39.0)	
Male	138 (61.0)	
Height (cm)	169.1±9.6	140-197
Weight (kg)	78.0±12.6	44-112
BMI	27.2±4.0	18-37.8

SD: Standard deviation, Min: Minimum, Max: Maximum, BMI: Body mass index, cm: Centimeter, kg: Kilogram

Table 2. Average laboratory findings of study population

	Mean±SD	Min-Max
Hb	14.4±1.6	9.9-18.1
WBC	7.15±1.91	3.36-12
PLT	248.6±63.4	135-622
INR	1.04±0.09	0.8-1.6
AST	18.5±5.7	10-41
ALT	22.8±14.1	3-103
ALP	72.8±24.4	6-242
GGT	20.8±15.7	3-111
Albumin	4.68±0.32	3.7-5.5
Total bilirubin	0.59±0.31	0.1-2.5
Bun	12.2±3.1	5-25
Creatinine	0.79±0.16	0.4-1.3
Na	140.1±2.2	135-146
K	4.4±0.3	3.5-5.5
FPG	95.2±9.5	71-168
Insulin	11.1±6.2	1.21-45.9
HbA1c	5.3±0.5	2.7-10
HOMA-IR	2.60±1.61	0.25-13.6
Total cholesterol	186.0±41.4	90-304
TGL	118.0±66.1	10-487
TSH	2.00±1.21	0.23-8.65
FT3	4.83±1.56	1.2-23
FT4	13.7±10.3	0.99-138

SD: Standard deviation, Min: Minimum, Max: Maximum, Hb: Hemoglobin, WBC: White blood cell, PLT: Platelet, INR: International normalized ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gama glutamyl transpeptidase, ALP: Alkaline phosphatase, Na: Sodium, K: Potassium, FPG: Fasting plasma glucose, HbA1c: Hemoglobin A1c, HOMA-IR: Insulin resistance, TGL: Triglyceride, TSH: Thyroid stimulating hormone, FT3: Free T3, FT4: Free T4

were divided into groups according to HS levels according to the liver biopsy results. Considering histopathological results, 42% of the donors had <5% HS, 58% of donors had ≥5% HS. According to the LAI calculated from CT images, 83 (36.7%) donors had <5% HS and 143 (63.3%) donors had ≥5% HS. MRI showed ≥5% HS in 203 (89.8%) donors and <5% HS in 23 (10.2%) donors (Table 3). Biopsy sensitivities for HS were 63.3% for CT and 89.8% for MRI, respectively (Table 3).

Table 3. Liver steatosis levels in invasive and non-invasive methods for study population

		n	%
Liver steatosis level at biopsy	<5%	95	42.0
	5-10%	53	23.5
	10-15%	37	16.4
	15-20%	17	7.5
	20-25%	5	2.2
	25-30%	8	3.5
	30-35%	6	2.7
	>35%	5	2.2
Liver steatosis on CT	No (<5%)	83	36.7
	Yes (≥5%)	143	63.3
Liver steatosis on MRI	No (<5%)	23	10.2
	Yes (≥5%)	203	89.8

CT: Computed tomography, MRI: Magnetic resonance imaging

Then, CT and MRI were compared to invasive liver biopsy, which is accepted as the gold standard method for the detection of HS level. Both CT and MRI showed a strong correlation with biopsy both in the detection of fatty liver and in the calculation of the amount of HS (p<0.001 for CT and p=0.003 for MRI) (Table 4).

Correlations were found between liver biopsy and CT, between liver biopsy and MRI, and between CT and MRI in the Spearman correlation analysis (r=0.452, r=0.438 and r=0.614, respectively, p<0.001) (Table 5).

Table 4. Comparison of radiological methods and liver biopsy for the detection of liver steatosis level in study population

		Steatosis in CT				p
		No		Yes		
		n	%	n	%	
Steatosis level at biopsy	<5%	50	60.2	45	31.5	<0.001
	5-10%	19	22.9	34	23.8	
	10-15%	8	9.6	29	20.3	
	15-20%	3	3.6	14	9.8	
	20-25%	1	1.2	4	2.8	
	25-30%	1	1.2	7	4.9	
	30-35%	1	1.2	5	3.5	
	>35%	0	0.0	5	3.5	
		Steatosis in MRI				p
		No		Yes		
		n	%	n	%	
Steatosis level at biopsy	<5%	17	73.9	78	38.4	0.003
	5-10%	5	21.7	48	23.6	
	10-15%	0	0.0	37	18.2	
	15-20%	1	4.3	16	7.9	
	20-25%	0	0.0	5	2.5	
	25-30%	0	0.0	8	3.9	
	30-35%	0	0.0	6	3.0	
	>35%	0	0.0	5	2.5	

CT: Computed tomography, MRI: Magnetic resonance imaging

Table 5. Correlation analysis of biopsy, computed tomography and magnetic resonance imaging in the detection of fatty liver

	Steatosis at biopsy		Steatosis at CT %	
	Rho	p	Rho	p
Steatosis at CT %	0.452	<0.001		
Steatosis at MRI %	0.438	<0.001	0.614	<0.001

CT: Computed tomography, MRI: Magnetic resonance imaging

DISCUSSION

LT is still accepted as the best treatment modality for ESLD. Due to insufficient number of cadaveric donors, LDLT has become the primary treatment option in worldwide. Donor HS is one of the most important limiting factors affecting the outcomes of LDLT. Using fatty graft is closely associated with the increased risk of post-operative complications in both donor and recipient. Severe HS is found to be associated with the delayed hepatic regeneration and increased risk of PNF. Therefore, accurate detection of HS in donors is one of the key points for the LDLT process[1,2].

Liver biopsy is still accepted as the gold standard method to evaluate HS but it has also many disadvantages[6]. CT has been used at many critical points such as volume and remnant calculation, evaluation of vascular structures and determination of HS in live liver donor candidates. Several studies have shown a strong correlation between liver biopsy and CT scan in the detection of HS in liver donor candidates[9,10]. Nowadays, CT scanning is accepted as a reliable alternative method to biopsy in many transplant centers in live liver donors.

In our study, CT showed a high correlation with both biopsy and MRI in the determination of liver fat in live liver donor candidates, consistent with the literature. Nevertheless, CT also has its own disadvantages. Notably, high dose radiation exposure is a serious limiting factor for both adults and children. HS measurement at CT depends on hepatic and

splenic attenuations. Hepatic attenuation may be adversely affected by the presence of copper, glycogen, iron, edema, or fibrosis in liver parenchyma. In addition, iron overload may mask the real HS rate and lead to misdiagnosis of HS. Because iron overload may increase the attenuation in liver parenchyma, coexistence of fatty infiltration and iron overload may lead nearly normal attenuation in the liver. Although CT is closely related to biopsy on the detection of liver fat, histological evaluation of the liver is not possible with CT scan. The detection of steatohepatitis requires histopathological evaluation of the liver by an experienced pathologist and this can be a disadvantage for the detection of potential liver damage at donor candidates. CT attenuation values also vary among the different manufacturers, CT scanners, and CT generations. Finally, different CT scan parameters (such as tube current, voltage, step) and patient-dependent parameters (such as BMI, length) can be listed as the other limiting factors for HS assessment with CT[11].

There are different MRI techniques that have been shown to be effective to detect HS in many studies[14,17,18]. MRI includes multiple measurement techniques such as MR spectroscopy (MRS), MR elastography (MRE), and chemical shift MRI for HS assessment. In a recent meta-analysis by Zheng et al.[19] the strength and accuracy of these three different MRI techniques in the detection of HS have been demonstrated. Chemical shift MRI is a measurement method based on the decomposition of liver signals into water and fat signals. It allows the evaluation of whole liver parenchyma. Thus, it is accepted as the most accurate MRI method for the evaluation of HS in many studies[19-22]. With this assumption, in our study, the formula specified in the material and method section, which correlates well with MRS in the determination of HS, was used to calculate the percentage of fatty liver tissue[17,18]. In the literature, some studies with MRS have found low accuracy in the determination of HS[23]. In addition, MRS requires the installation of additional technical sequences and specific and expensive softwares that extend the MRI processing time. In some studies, it has been shown that MRE has low sensitivity in the detection of HS[24]. Therefore, chemical shift MRI seems to be the most accurate and feasible MRI method for the assessment of HS in current literature. In our study, the MRI images of donor candidates were retrospectively scanned, and their HS levels were determined by chemical shift MRI method. HS levels calculated with chemical shift MRI method were highly correlated with both invasive biopsy and CT scan. Our study confirmed the accuracy and sensitivity of chemical shift MRI method in the detection of HS in donor candidates.

HS can be seen in approximately 25% of live liver donor candidates[19]. Donor candidates with significant HS should be prepared for operation using dietary changes, physical exercises and medical treatments prior to transplantation. It is important to re-evaluate donor candidates who can lose weight through diet and other ancillary methods in terms of HS before transplantation and CT is the most common non-invasive method used in many transplant centers for this purpose. The use of recurrent CT scans in donor candidates also means giving high-dose and redundant radiation to healthy individuals. Future medical problems that can be caused by recurrent CT scans in donor candidates are uncertain. Therefore, MRI can be a useful alternative method with the same efficacy as CT, especially in donors requiring post-dietary liver fat control.

Calculation of proton density fat fraction (PDFF) is a recently described chemical shift-based water and fat separation technique that can be performed by magnitude and complex based techniques. The complex-based technique uses both magnitude and phase images, and magnitude-based techniques use only magnitude images for PDFF calculation. This is a promising method that can be completed in a breath hold and allows for the simple calculation of fat fraction in any segment of the liver. The advantage of this technique versus older MR imaging techniques (Dixon and fat saturation methods) is that this technique provides the correction of factors that influence MR SI, such as T1 bias, T2* decay, spectral complexity of fat, noise bias, and Eddy currents. This technique has been shown to provide accurate quantification of hepatic fat content compared to MRS[21,25-28]. Idilman et al.[29] found a good correlation in the comparison of PDFF measurements with biopsy results in their study. PDFF distinguished moderate or severe steatosis from mild or no steatosis with 93.0% sensitivity and 85.0% specificity.

In the meta-analysis performed by Gu et al.[30], the degree of hepatic steatosis corresponding to <5%, 5-33%, 33-66% and >66% steatosis was defined as 0, 1, 2 and 3 according to the Non-alcoholic Steatohepatitis Clinical Research Network histological scoring system for non-alcoholic fatty liver disease (NAFLD). This meta-analysis contains 6 original articles (635 patients) and has sufficient data to investigate the diagnostic performance of MRI-PDFF in steatosis classification. In this study, the summary AUROC values of MRI-PDFF in steatosis grades 0 versus 1-3, 0-1 versus 2-3, and 0-2 versus 3 were significantly higher, similar to previous studies. In addition, they found that with increasing liver fat content, overall sensitivity and specificity decreased, indicating lower accuracy of MRI-PDFF in patients with severe hepatic steatosis. In summary, this meta-analysis shows that MRI-PDFF is a sensitive and non-invasive diagnostic method for classifying the degree of hepatic steatosis in patients with NAFLD.

Study Limitations

Limitations of this study include possible population bias toward a cohort of individuals considering living related liver donation, its retrospective design and small sample size, and

wide range of time between liver biopsy and CT scanning. Furthermore, the liver biopsy specimens were acquired only from the right hepatic lobe, whereas the mean hepatic attenuation and SI were acquired from 10 ROIs of both hepatic lobes. Therefore, it is thought that there may be some degree of sampling error in hepatic needle biopsy.

CONCLUSION

Donor HS is a limiting factor for LDLT. CT is still an inevitable option for liver volume calculation and evaluation of vascular structures during the pre-transplant period. CT is also highly correlated with biopsy in the detection of HS. Donor safety is the most important ethical problem in LDLT. Recurrent CT scans for the evaluation of HS can lead to damage in donor bodies because of unnecessary radiation exposure in the following years. MRI showed its own strength and accuracy in the detection of HS in donor candidates in our study. Our study demonstrated that MRI might be a powerful alternative to CT for donor candidates with HS in the pre-transplant period, who needed to control HS after diet and other treatments. Future studies can provide new and beneficial findings in this issue.

Ethics

Ethics Committee Approval: This study was approved by Demiroğlu Bilim University institutional review committee and protocol review committee (2019-16-03).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.Ş., A.O., E.K., Concept: B.K.S., T.Ş., A.O., E.K., Design: B.K.S., T.Ş., Data Collection or Processing: B.K.S., T.Ş., Analysis or Interpretation: B.K.S., T.Ş., A.O., E.K., Literature Search: B.K.S., T.Ş., A.O., E.K., Writing: B.K.S., T.Ş., A.O., E.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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